POTENTIAL DRUG INTERACTIONS IN INTENSIVE CARE PATIENTS AT A TEACHING HOSPITAL

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This study assessed potential drugs interactions in intensive care patients at a university hospital in Ceará, northeast Brazil. Of 102 patients studied, 72.5% were exposed to 311 potential drug-drug interactions; 64% of them were females aged 60 years or more and hospital stay was at least 9 days. A statistically significant association was found between number of drugs used and the occurrence of drug interactions. A total of 1,140 drugs were scheduled to be administered concomitantly; of these, 74% had potential for drug interactions. As for the classification of these events, 48.2% had a pharmacokinetic profile; 55.4% were of slow onset; 54.7% had moderate severity; and 60.6% were well-documented in the literature. The most common clinical action taken was "to monitor signs and symptoms". Nursing staff can perform 80% of preventive actions to avoid undesirable effects of drug interactions. However, nurses need to have adequate knowledge about drug action mechanisms and triggering factors associated to drug interactions.

DESCRIPTORS: intensive care units; drug interactions

INTERACCIONES MEDICAMENTOSAS POTENCIALES EN PACIENTES DE UNA UNIDAD DE TERAPIA INTENSIVA DE UN HOSPITAL UNIVERSITARIO

Este estudio investigó interacciones medicamentosas (IM) potenciales en una Unidad de Terapia Intensiva (UTI) en un hospital universitario del Ceará. De los 102 pacientes del estudio, 72,5% presentaron 311 potenciales IMs. De estos, 64% eran del sexo femenino, con edad mayor o igual a 60 años y tiempo de internación mayor o igual a nueve días. Hubo una asociación estadísticamente significativa entre el número de medicamentos y la ocurrencia de IM; 1.140 medicamentos fueron administrados durante el mismo horario, entre estos, 74% presentaron potencial para IM. En lo que se refiere a la clasificación de las IMs, 48,2% presentaron un perfil fármaco cinético, 55,4% inicio demorado, 54,7% moderada gravedad y 60,6% bien documentadas en la literatura. El manejo clínico más frecuente fue "observar señales y síntomas". Ochenta por ciento de las intervenciones para evitar los efectos indeseables de las IMs pueden ser realizadas por el enfermero. Sin embargo, para que estas ocurran, de hecho, es importante que el enfermero conozca los mecanismos farmacológicos de las IMs, así como sus factores precipitantes.

DESCRIPTORES: unidades de terapia intensiva; interacciones de drogas

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Este estudo investigou interações medicamentosas (IM) potenciais em uma Unidade de Terapia Intensiva (UTI) de um hospital universitário do Ceará. Dos 102 pacientes do estudo, 72,5% apresentaram 311 potenciais IMs. Desses, 64% eram do sexo feminino, com idade maior ou igual a 60 anos e tempo de internação maior ou igual a nove dias. Houve associação estatisticamente significativa entre o número de medicamentos e a ocorrência de IM, e 1 140 medicamentos foram aprazados no mesmo horário. Desses, 74% apresentaram potencial para IM. Quanto à classificação das IMs, 48,2% apresentaram perfil farmacocinético, 55,4% início demorado, 54,7% moderada gravidade e 60,6% bem documentadas na literatura. O manejo clínico mais freqüente foi "observar sinais e sintomas". Oitenta por cento das intervenções para evitar os efeitos indesejáveis das IMs podem ser realizadas pelo enfermeiro. No entanto, para que essas ocorram, de fato, é importante que o enfermeiro conheça os mecanismos farmacológicos das IMs, bem como seus fatores precipitantes.

DESCRITORES: unidades de terapia intensiva; interações de medicamentos

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INTRODUCTION

Drug-drug interaction is an event that occurs when the effects of a drug are modified when another drug or food is taken concomitantly. This interaction can cause reduced, null or increased drug effect[1]. Interactions can be classified, according to mechanisms by which drugs interact with each other, as physical-chemical, pharmacokinetic and pharmacodynamic. Physical-chemical or pharmaceutical interaction occurs when two or more drugs interact exclusively due to physical-chemical mechanisms. Pharmacodynamic interaction occurs when there is an added or antagonistic effect of drugs. Pharmacokinetic interaction occurs when a drug acts modifying absorption, distribution, biotransformation, and elimination[2] of another drug.

Risk factors for drug interactions can be related to patient, drug and medical prescription. Patient-related factors include people that are more vulnerable to drug interactions such as the elderly, patients undergoing surgical procedures, those receiving intensive care (ICU), and immunosuppressed patients. The main drug-related risk factors are drug potency to cause effects of enzyme induction and inhibition, and drug therapeutic index, i.e. the ratio of the maximum tolerated dose to the therapeutic dose. Risk factors related to medical prescription include a large number of prescription drugs needed for patients admitted to the hospital with complex clinical conditions[3-4].

The occurrence of drug interactions exponentially increases as the number of drugs prescribed increases[5]. It is estimated that drug interactions occur in 3% to 5% of patients receiving a small number of drugs, and increase to 10% to 20% in patients receiving 10 to 20 drugs[6]. As inpatients receive on average seven different drugs a day, drug interaction is evidently a significant concern, even more in ICU settings where critical patients receive care and a large range and quantity of drugs on a daily basis.

Although drug interactions have been widely addressed in medical and pharmaceutical books and journals, there have been scarce investigations in the nursing area, especially bearing in mind that the nursing team is responsible for the entire drug administration process. Thus, to further explore this subject, a study was conducted to assess potential drug interactions in ICU patients in a hospital in the state of Ceará, northeast Brazil. Studies on drug interactions focusing on nursing clinical practice are important as a useful tool for decision making during the drug administration process.

METHODS

Descriptive, exploratory, cross-sectional study carried out in an ICU of a university hospital in Ceará. All medical records of patients who were admitted to the hospital ICU between June 2006 and June 2007 were reviewed. Patients who met the following criteria were included: being over 18 years of age, and at least 6-day stay in ICU. The latter inclusion criterion was established as all drugs prescribed on Day 2 and on Day 6 of ICU admission were recorded for analysis. These days were selected because the majority of drugs are prescribed on Day 1 of ICU admission, and most therapeutic adjustments are made during this first week of admission.

Of 362 patients admitted to ICU over one-year period, 102 of them met the inclusion criteria. The study was approved by the institutional Research Ethics Committee of the study site (Process No. 050.06.02).

Data was collected using a questionnaire that comprised two sections: section I included demographic and patient identification information such as name (initials), age, gender, and information about ICU admission such as medical diagnoses on Day 2 and Day 6, date of admission, and ICU stay. Section II included information on drugs prescribed and administration times.

The statistical analysis was performed using SPSS® software v. 15.0. The chi-square test for independence was used to test the association between the variables age, gender, hospital stay, number of drugs used, and medical diagnosis. A 5% significance level was set. Drug interactions were analyzed using Drug-Reax® System database from Micromedex®[7]. Potential drug interactions identified in the study were classified by severity (minor, moderate, major, and contraindicated), onset of action (fast, slow, and indeterminate), documentation (excellent, good, satisfactory, poor, and unknown), and pharmacokinetic and pharmacodynamic profile.

In regard to severity, interactions were classified as major, when they were life-threatening and required immediate medical intervention; moderate, when they aggravated the patient's condition and required drug therapy change; minor, when patients experienced any change in their clinical condition but did not require drug therapy change; and contraindicated, when concomitant drug administration was not recommended[7].

As for onset of action, i.e. the expected time between therapy start and the occurrence of adverse events, drug interactions were classified as fast, when adverse events due to drug-drug interaction occurred within 24 hours; slow, when adverse events occurred within more than 24 hours; and indeterminate, when the time for onset of adverse events after concurrent administration of drugs[7] was not documented in the literature.

With respect to drug interaction documentation, it was classified as excellent, when there were controlled clinical studies evidencing drug-drug interactions; good, when documentation about interaction was available but no controlled clinical studies; satisfactory, when few studies evidenced interaction but there were available pharmacological considerations about drug interactions; poor, when documentation was limited to case reports; and unknown, when there was no documentation in the literature evidencing drug interaction[7].

Drug interactions were further classified according to the mechanism of interaction. Pharmacokinetic interaction occurred when a drug was likely to interfere with absorption, distribution, metabolism, and elimination of another drug and pharmacodynamic interaction occurred when drugs had similar or antagonistic effects[7].

RESULTS

Of 102 patients studied, 66 (64.7%) were males. Their age ranged between 18 and 96 years, median 60 years (interquartile range: 41–70 years). They stayed in the ICU at least five days and no more than 163 days, median stay nine days (interquartile range: 6–16 days).

As for the number of drugs prescribed on a normal day, patients received one to 19 drugs on Day 2, and one to 17 drugs on Day 6, median nine drugs for both days. The number of diagnoses ranged from one to six on Day 2, and one to seven on Day 6, median three diagnoses for both days. The most common diagnostic classes were cardiovascular diseases (152; 24.9%), notably systemic arterial hypertension (37; 6%), and respiratory diseases, especially acute respiratory failure (74; 12.1%).

In total, 1,845 drugs were identified in the medical records examined, of which 924 on Day 2 and 921 on Day 6 of admission. They comprised 137 different drug varieties.

The Anatomical Therapeutic Chemical (ATC) Classification System[8] was used for the classification of drugs. Drugs in the anatomical group "alimentary tract and metabolism" were more frequently seen on both days evaluated (474; 25.7%); followed by "anti-infectives for systemic use" (344; 9.9%); "cardiovascular system" (243; 13.1%) and "nervous system" (222; 12%). In each drug class, the most prescribed drugs were: ranitidine (84; 17.7%); cefepime (64; 8.6%); furosemide (2; 17.2%), and fentanyl (80; 36%).

The preferred administration route on Day 2 and Day 6 was intravenous (1,151 drugs administered; 62.3%); followed by oral administration (366; 19.8%); inhalation (204; 11%); and subcutaneous (121; 6.5%). Sublingual was seen in one case and intramuscular in two cases.

As for administration times, of 1,845 drugs studied, 1,140 (61.8%) were scheduled concomitantly, and 844 (74%) of them showed potential for drug interactions. Drugs were most often administered at 6 am, and up to nine drugs were administered at the same time.

Of 102 patients studied, 74 showed 311 potential drug interactions, averaging three interactions per patient (standard deviation [SD]: 3.7). Drug interactions were most commonly seen in female patients (47–64%), aged 60 or more (38–51.3%), and in those who stayed in ICU for at least nine days (42–56.7%) (Table 1).

An association was found between females and drug interactions (p=0.004/95% CI: 0.095–0.74). As for age and hospital stay, no association was found with drug interactions.

Table 1 – Association between the variables age, gender, and hospital stay and drug interactions. Fortaleza, Brazil, 2007

Variables	Number of patients		Odds ratio (95% CI*)	p-value
	Interaction (n=74)	No interaction (n=28)		
Gender				
Male	27	19	0.27 (0.095-0.74)	0.004
Female	47	9		
Age				
<60	36	14	0.94 (0.36-2.47)	0.90
≥60	38	14		
ICU stay				
<9	32	15	0.66 (0.25-1.7)	0.35
≥9	42	13		

*CI: confidence interval

The variables medical diagnosis and number of drugs used were analyzed on Day 2 and Day 6 separately, since they were different on these days. It was found, however, that 71 patients (69.6%) had less than three diagnoses on Day 2, 39 (55%) of whom had drug interactions. On Day 6, most patients had at least three medical diagnoses (77–75.5%), 40 (52%) of whom had drug interactions. Mean number of medical diagnoses per patient showing drug interactions was 2.8 on Day 2 and 3.3 on Day 6, median three diagnoses for both days. However, no association was seen between number of drug interactions and number of diagnoses (p=0.99) (Table 2). The most common diagnostic classes on Day 2 and Day 6 were: cardiovascular (122; 26.6%), respiratory (115; 25.1%), and gastrointestinal diseases (45; 9.8%).

Table 2 – Association between the variables number of drugs used and number of diagnoses on Day 2 and Day 6 of ICU admission and drug interactions. Fortaleza, Brazil, 2007

Variables	Number of patients: Interaction	n	No interaction	n	Odds ratio (95% CI)	p-value
Number of diagnoses (Day 2)						
<3	39	59	32	43	0.67 (0.25-1.73)	0.36
≥3	20		11			
Number of drugs (Day 2)						
<9	21	59	22	43	0.52 (0.21-0.26)	0.11
≥9	38		21			
Number of diagnoses (Day 6)						
<3	13	53	12	49	1.0 (0.36-2.74)	0.99
≥3	40		37			
Number of drugs (Day 6)						
<9	14	53	30	49	0.22 (0.08-0.56)	0
≥9	39		19			

As for the number of drugs prescribed, patients who potentially had drug interactions received 1,137 drugs, while those who did not potentially have drug interactions received 437 drugs. Those who received nine or more drugs had a higher rate of drug interactions on both days studied. Yet, at a 5% significance level, an association between number of drugs prescribed on Day 6 and occurrence of drug interactions (p<0.001) was found.

Of 311 potential drug interactions identified, nervous system drugs accounted for 125 (40%). Midazolam was the most common associated drug (65–28%). Among the most interacting drugs, midazolam and fentanyl were associated to 45 (14.5%) identified drug interactions.

In regard to the classification of potential drug interactions identified in the study, 189 (60.6%) had good documentation, 170 (54.7%) were of moderate severity, and 173 (55.4%) of slow onset. And the majority was classified as pharmacokinetic interactions (150–48.2%).

Among actions that can be taken to minimize or even prevent the effects of drug interactions, 80% can be performed by nursing staff: monitor signs and symptoms (211; 47.9%); monitor the therapeutic response (95; 20.6%); adjust administration time (38; 8.2%); and avoid drug combination (15; 3.3%).

DISCUSSION

As for sociodemographic characteristics, an association was found between female gender and drug interactions. This association may be explained by the fact that most patients studied were women and that, thus, they received a larger number of drugs than men.

Potential drug interactions were most commonly seen among those aged 60 or more (38; 51%). Similarly to gender, age is regarded as a risk factor for drug interactions. Drug interactions are more frequent in patients over 60 because they suffer from chronic conditions requiring multidrug therapy. The elderly are also more susceptible to drug interactions due to deterioration of liver and kidney function, as well as reduced drug metabolism and elimination[9].

As for hospital stay, higher rates of drug interactions (56.7%) were seen in patients who stayed in ICU for longer than nine days.

The most common diagnostic classes with potential for drug interactions were cardiovascular diseases (122, 26.6%), especially arterial hypertension (5.1%). Cardiovascular, renal and endocrine diseases may be directly associated to the occurrence of drug interactions due to factors associated to patient characteristics and the drugs used for their treatment[10].

In regard to the number of drugs prescribed on Day 2 and Day 6, a positive association was found between the number of drugs prescribed and potential drug interactions on Day 6 of ICU admission ($p<0.001$). This association is corroborated in many studies[3,11-12]. However, in addition to the number of drugs prescribed, many of them were administered at the same time and through the same route, which very likely may have precipitated drug-drug interactions.

With respect to administration times, of 1,845 drugs studied, 1,140 (61.8%) were scheduled to be administered concomitantly. Of them, 844 had potential for drug interactions. Most drugs were administered between noon and 4 p.m., but the most frequent administration time was 6 a.m., when up to nine drugs were administered at the same time. This finding is corroborated by another study investigating potential drug interactions in cancer patients based on nursing administration schedule. Higher drug administration was reported in the evening (58.8%) and larger number of doses at 10 p.m. (39.6%)[13].

Few studies on drug interactions have investigated drug administration time schedule as a risk factor for drug interactions. Time schedule follows the facility's standard procedure, disregarding the chance of drug-drug-interactions. It should be mentioned that, in the facility studied, nurses were responsible for establishing drug administration time schedules. This is not the current practice in hospital settings, however, being a task assigned to either nursing assistants and/or ICU clerical staff in many instances.

As for routes of drug administration, most drugs were administrated intravenously (1,151; 62.3%) as expected, because it is the preferred route in ICU patients, since most are severely ill and require a fast route for immediate drug effects. The second most common route was orally (19.8%). Although most drugs were not administered orally, this finding is remarkable because it makes us question how drugs are being prepared and administrated to patients, as most of them are receiving oral drugs through a nasogastric tube.

It was found that 125 potential drug interactions (40%) were associated to drugs acting in the central nervous system. Notably, midazolam was identified in 20.8% of these events, followed by fentanyl (6.7%).

In regard to the most common drug interactions, 14.5% were attributed to the association between midazolam and fentanyl. This is the most severe interaction and has been well documented in the literature. The association of these drugs had addictive effects on the central nervous system and can lead to respiratory depression[7]. Yet, the expected time lag for the development of related adverse events has not been clarified. But when these two drugs are concomitantly administered, it is recommended to carefully monitor the patient, preferably in an ICU setting. In addition to ongoing patient monitoring, dose reduction of one of these drugs, or both of them, is recommended to minimize the effects of this drug combination[7].

In conclusion, most potential drug interactions identified in the present study had slow onset (173; 55.4%), moderate severity (170; 54.7%) and were well-documented in the literature (189; 60.6%). The majority were pharmacokinetic (150; 48.2%), followed by pharmacodynamic interactions (138; 44.4 %), and 23 (7.4%) were classified as unknown, i.e. the underlying mechanism of interaction was not clear.

It is crucial that health providers are able to identify and classify drug interactions, and know how to clinically manage them, that is, how to minimize or even prevent them. Of 311 drug interactions identified, 461 clinical management actions were taken, with up to three actions per interaction. The main actions identified were: monitor signs and symptoms (211; 47.9%); monitor the therapeutic response (95; 20.6%); adjust dose (85; 18.4%); adjust administration time (38; 8.2%); avoid drug combination (15; 3.3%); replace drug (4; 0.9%); and change administration route (3; 0.7%).

Although not all drug interactions are preventable, dissemination of knowledge among health providers about the main risk factors for drug interactions and their mechanisms of interaction, together with information about the most common drug interactions that are clinically relevant, is key to prevent these events. This knowledge will enable health providers to choose therapeutic regimens and drug administration times that are safer for patients, providing better quality care and preventing damages.

REFERENCES

1. Hartshorn EA. Drug Interaction. Ann Pharmacother 2006; 40(1):112-3.

2. Oga S, Basile, AC, Carvalho FM. Guia Zanini- Oga de interações medicamentosas. 7ª ed. São Paulo: Atheneu; 2002.

3. Egger SS, Drewe J, Schlienger RG. Potential drug-drug interactions in the medication of medical patients at hospital discharge. Eur J Clin Pharmacol 2003; 58(11):773-7.

4. Kohler GI, Bode-Boger SM, Busse R, Hoopmann M, Welte T, Böger RH. Drug-drug interactions in medical patients: effects of in hospital treatment and relation to multiple drug use. Int J Clin Pharmacol Ther 2000; 38(11):504-13.

5. Ceia, F. Interacções medicamentosas na prática clínica. Rev Port Clin Geral 2007; 23:197-207.

6. Bustamante GDD, Cabrera C, Duran GMG, Nunez MTJ. Detección de interacciones medicamentosas, em pacientes ingresados a la unidad de cuidados intensivos del Instituto Autônomo Hospital Universitário de los Andes. Vitae Academia Biomédica Digita 2005; 25(7):1-16.

7. Midromedex Healthcare Series: Interactions. [Acesso em: 10 out. 2007]. Disponível em: https://www.thomsonhc.com/hcs/librarian/PFDefaultActionId/pf.LoginAction/ssl/true?login.password_index_0=v87o9b42e7&login.username_index_0=C7A0P7E7S&ND_CPR=Login.

8. World Health Organization (WHO). Anatomic Therapeutic and Chimical Classification of Drugs. 2003. [Acesso em: 14 out. 2007]. Disponível em: http://www.who.int/classifications/atcddd/en/.

9. Malone DC, Abarca J, Hansten PD, Grizzle A J, Armstrong EP, Van Bergen RC, et al. Identification of serious drug-drug interactions: results of the partnership to prevent drug-drug interactions. J Am Pharm Assoc (Wash DC) 2004; 44(2):142-51.

10. Goldberg RM, Mabee J, Chan L, Wong S. Drug-drug and drug- disease interactions in the ED: Analysis of a high-risk population. J. Emerg. Méd 1996; 14 (5):447-50.

11. Sehn R, Camargo AL, Heineck I, Ferreira MBC. Interações Medicamentosas potenciais em prescrições de pacientes hospitalizados. Infarma 2003; 15(9-10):77-81.

12. Calvet A, Diez de Ulzurrum M, Perez MT, Esteras J. Interacciones farmacológicas in tratamientos crónicos: medidas correctoras para su prevención en un área básica de salud rural. Atenção Primaria 2001; 27(1):33-37.

13. Secoli SR, Padilha KG. Polifarmácia em Leucemia Mielóide Aguda: Administração e Interação de Medicamentos. Prática Hospitalar 2005; 37(7):78-85.

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